EPITHELIOMA ATTRIBUTABLE TO ARSENIC*

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A previous investigation of the arsenical type of superficial epithelioma made by one of us (1) (H. M.) revealed the pertinent clinical, histopathologic, histochemical and chemical features of this entity. In the report of this study emphasis was given to the fact that the epithelioma provoked by ingestion of arsenic differs from the lesions of superficial epitheliomatosis (2) and Bowen's disease (3), and that by proper evaluation of various findings the distinction usually can be made in each case.

In the interim since this report was published studies along the same lines have been continued. We shall report briefly the accumulated results of further observations, which in general confirm the conclusions in the earlier paper. At this point it should be stated that the nature of the action of arsenic is obscure and that little has been written in recent years on the rôle of arsenic as a carcinogenic agent. We are in accord with the suggestion of Cook and his colleagues (4) that arsenic is deserving of more attention by workers engaged in cancer research.

MATERIAL AND FINDINGS

Our additional material includes six cases of superficial epithelioma induced by arsenic in which biopsies of skin were obtained; two cases in which arsenical epitheliomas were associated

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† Work done in part while a Fellow in Dermatology, Mayo Foundation.

with lesions of superficial epitheliomatosis, and fourteen cases of superficial epitheliomatosis. Most of these lesions were studied both by the methods of quantitative chemical analysis (5) and histochemical examination (6).

Specimens for biopsy were obtained in cases of superficial epitheliomatosis so that a control group of observations might be available for comparison with those made in the cases of arsenical epithelioma. As would be expected, most of the lesions of superficial epitheliomatosis were of the basal cell type, a form which, as has been emphasized in a previous report, rarely occurs in response to the action of arsenic. In only one instance could arsenic be demonstrated in the tumor. It is, therefore, evident that arsenic occurs exceptionally in lesions of superficial epitheliomatosis. However, the presence of arsenic in the tissue does not predicate the diagnosis of arsenical epithelioma in the absence of other essential factors.

In the cases of arsenical epithelioma, our findings were similar to those recorded previously: arsenic was present in every lesion examined and could be demonstrated by either chemical or histologic technic. In every case, Osborne's method gave positive results, and comparison with adjoining normal skin showed a greater concentration of arsenic in the epithelioma. It happens, however, that this histochemical finding was not always corroborated by the quantitative chemical procedure, probably because the specimens of tissue in some instances were so small and the amount of the arsenic reported therein so tiny.

CLINICAL AND HISTOPATHOLOGIC ASPECTS

The following cases are cited to illustrate certain of the features encountered in the study of these lesions:

Case 1. A man, aged forty-nine years, who registered at the Mayo Clinic on January 20, 1938, had had psoriasis since the age of seventeen years. In 1912 Fowler's solution (solution of potassium arsenite, U.S.P.) had been administered for treatment of the psoriasis, and until 1932 a course of the medication was repeated at least once yearly, always with beneficial effects on the psoriasis. In 1927 keratoses first appeared on the palms and soles. Fifteen months before the patient came to the clinic, a verrucous lesion on one thenar eminence became

ulcerated, and subsequently others of the keratoses enlarged and broke down. These were treated by his physician in his home locality.

Examination at the clinic disclosed two elevated, firm, tender keratotic nodules on the left palm, many palmar keratoses, a papillomatous lesion on the right temple, with pearly telangiectatic border, and numerous firm infiltrated crusted plaques with pearly telangiectatic borders over the trunk and upper extremities. A subcutaneous plaque about 2 cm. in diameter was present over the right cheek, just lateral to the bridge of the nose, and corresponding to it, a tumor protruded into the anterior portion of the right nasal fossa. Extensive patches of psoriasis covered the trunk, extremities, and also the face and scalp; the nails were altered typically. The patient volunteered the information that the lesions of the palms and soles and the crusted lesions of the trunk differed in appearance from those of psoriasis. There was no question of origin of new growth on a pre-existing psoriatic plaque.

The tumors (as well as the keratoses) were excised or destroyed by fulguration and electrocautery. Those on the trunk disclosed the histologic structure of squamous cell epithelioma, grade 2, of the arsenical type; some also contained a few areas of basal cell epithelioma. The plaque on the right cheek proved to be of basal cell origin, and that in the right nasal fossa was reported by the surgical pathologist as a "very inflammatory degenerating carcinoma, probably of basal cell type."

By chemical analysis of the excised epitheliomas, the presence of arsenic was demonstrated in each specimen; the quantity varied from 0.00024 to 4.3 mgm. per gram of tissue. Examination of normal skin revealed 0.00008 mgm. of arsenic per gram of tissue. Arsenic was not detected in the urine.

In July, 1938, a pearly nodule was excised by the patient's physician from the scar on the left thenar eminence. This proved microscopically to be squamous cell epithelioma, grade 2. With the Osborne method crystals of arsenic trisulfide were demonstrable in the epidermis; these were concentrated much more abunddantly in the area occupied by epithelioma than in the adjacent normal epidermis.

Arsenic as indicated in case 1 may appear in varying concentrations in different lesions on the same person. That arsenic is deposited erratically in the epithelial structures is indicated by the following observations: 1) analyses of skin, hair and nails may fail to disclose arsenic despite known ingestion of the agent; 2) hair and also urine of the patient often do not yield any evidence of arsenic on analysis even when the epithelioma and adjoining normal skin give positive results, and 3) occasionally the hair may contain appreciable amounts of arsenic when skin and nails have none. The factors which account for the distribution of arsenic in the tissues and in the cutaneous appendages are not yet known.

Case 2. A woman, aged sixty-nine years, who registered at the Mayo Clinic on February 6, 1935, had numerous keratotic and crusted nodules on the trunk and extremities, in places distinctly grouped. The duration of this condition was given as two years. Removal of crusts resulted in bleeding. A verrucous lesion had been present on the left fifth finger for five years; roentgen therapy was administered at one time without healing the lesion. Plaques with a fine threadlike border were not observed.

Doses of a solution of potassium arsenite had been taken for nine months in 1915, for five weeks in 1932 and for one week in December, 1934. The general examination of the patient did not reveal any significant abnormalities aside from those on the skin.

Excision and examination of lesions on the trunk and arms revealed them to be squamous cell epitheliomas, grade 1 and 2, with intracellular vacuolation in addition to distinct Bowen-like features. Crystals of arsenic trisulfide were found in all sections stained by Osborne's method. Two lesions on the trunk, one, squamous cell epithelioma, grade 1 and the other, grade 2 when subjected to chemical analysis, yielded respectively 0.275 and 0.022 mgm. of arsenic per gram of tissue. From a fragment of unaffected skin, weighing 10 mgm., it was calculated that the skin contained 1 mgm. of arsenic in each gram. It is probable, however, that a technical error accounted for this high figure. The specimen was small for estimation of its arsenic content to be reliable. With Osborne's stain only a few crystals were observed in the section.

The left fifth finger was amputated. Microscopically the lesion was shown to be squamous cell epithelioma, grade 1. One examination of the complete output of urine for twenty-four hours for arsenic gave negative results.

Two aspects are deserving of mention in this case: 1) the disparity, already alluded to, between the quantitative arsenic content of the tumors and of normal skin, and 2) the absence of arsenical keratoses on the palms or soles, and of other features of arsenic intoxication such as pigmentation and hepatitis. Focal concentrations of arsenic may occur in the skin without development of epithelioma. We have found, by chemical examination, that arsenic is occasionally present in appreciable quantities in the skin in a variety of noncarcinomatous diseases of the skin. It is hardly likely that the mere presence of arsenic in these cases need signify the possibility of future epitheliomatous change. With regard to the second point, it may be remarked that many of the lesions were clinically and histologically analogous to keratoses (figs. 1 and 2*a*).

Case 3 illustrates that a history of ingestion of, or exposure to, arsenic is not always obtainable, even in the presence of unim-

peachable evidence of arsenical sequelae, and also that arsenical epitheliomas on the trunk may be limited to a few solitary lesions.

*Case 3.** A dentist, sixty-seven years of age, was seen in the Department of Dermatology of the Research and Educational Hospitals of the University of Illinois on March 15, 1934, for treatment of two crusted superficial epitheliomas on

FIG. 1 (case 2). Group of arsenical epitheliomas on arm simulating arsenical keratoses of palms or soles, both clinically and pathologically (see figure 2*a*) and large lesion on abdomen simulating Bowen's disease. Note absence of thread-like pearly border.

the back. The lesions, described as arciform in configuration, had been present for two or three years. Keratoses on the palms and soles apparently were not noted. Treatment consisted of applications of solid carbon dioxide and additional destruction with the actual cautery.

The patient was seen again on February 25, 1941, because of a crusted ulcer on the left index finger; this had appeared four years previously. Numerous arsenical keratoses were present on the palms, and a few were observed on the soles. The two circular, superficial epitheliomas had recurred at the site of

* This case is reported with permission of Dr. Francis E. Senear, head of the Department of Dermatology, University of Illinois College of Medicine.

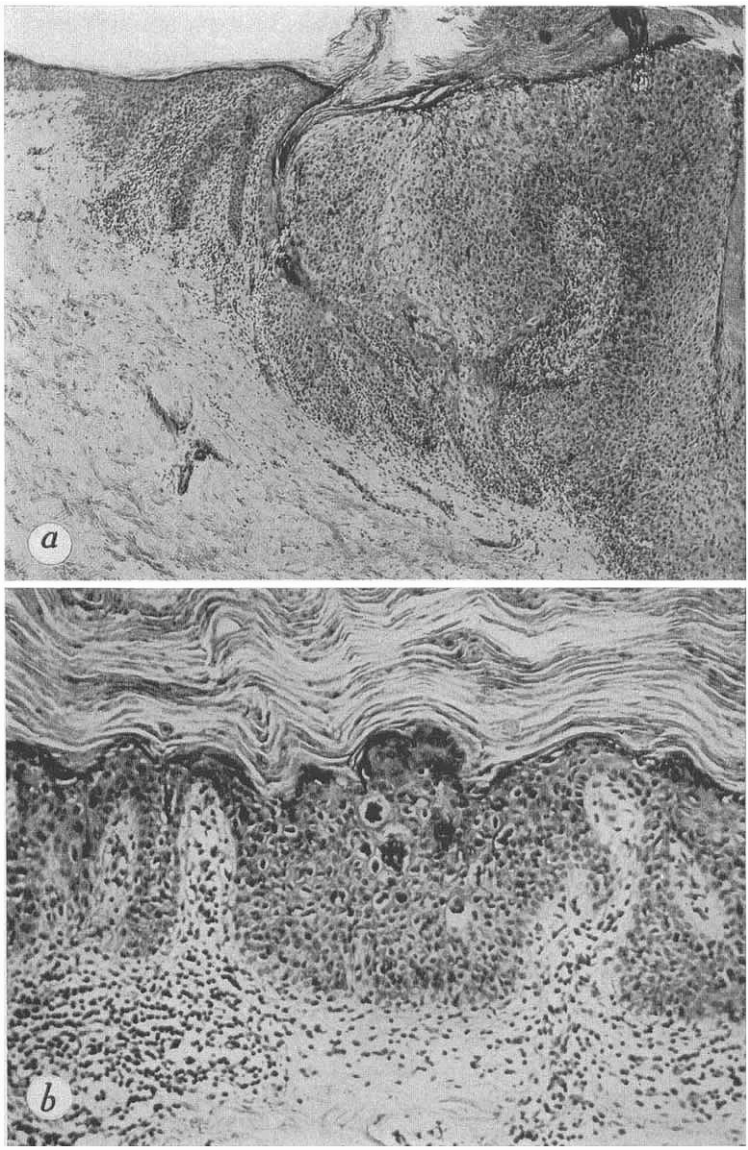

FIG. 2*a*. Keratosis on arm, same lesion as shown in figure 1; histologically squamous cell epithelioma, grade 2, with malignant dyskeratosis, vacuolation of epithelial cells and giant cells and early invasion of cutis; *b*, arsenical keratosis squamous cell epithelioma, grade 1 in situ, simulating the histologic picture of Bowen's disease with malignant dyskeratosis, giant epithelial cells and epithelial giant cells.

previous treatment on the back. Careful questioning did not elicit any information with regard to ingestion of arsenic at any time in the past.

The lesions on the back were excised, and the one on the finger was removed with the cautery. Microscopic sections showed in each site squamous cell epithelioma, grade 1, with Bowen-like features. Quantitative analysis of the tissue for arsenic was performed in the laboratory of the coroner of Cook County through the courtesy of Dr. Clarence W. Muehlberger, coroner's toxicologist, with the following results: (1) epitheliomas from the back contained 0.0026 mgm. of arsenic per gram of tissue; (2) epithelioma from the finger, 0.020 mgm. of arsenic per gram of tissue; and (3) normal skin, 0.0019 mgm. of arsenic per gram of tissue. Osborne's stains demonstrated crystals of arsenic trisulfide within the epitheliomas.

The appearance of palmar and plantar keratoses induced by arsenic is sufficiently familiar to make its description unnecessary. The early microscopic changes in the malignant alteration of arsenical keratosis consist of keratinization and vacuolation of individual cells in the epidermis (malignant dyskeratosis, fig. 2*b*). Clinically this is manifested by growth and ulceration of the keratosis. Further development results in features of penetration and invasion, when the continuity of the basal cell layer is destroyed, so that squamous cell epithelioma, grade 2 or 3, is recognized. We have not seen basal cell epithelioma arising from arsenical keratosis but possibly such an event may rarely occur (7). In the areas of proliferation of the prickle cells are numerous vacuolated cells, twice or three times as large as the normal cells, with small, irregular, deeply staining nuclei. They resemble the clear cells of Paget's disease of the nipple, except that intercellular bridges are present. The vacuolation is not caused by ordinary edema but represents, like isolated keratinization, a phenomenon of dyskeratosis. Another feature is the presence of giant cells induced by clumping of epithelial cells or by amitosis. A dense infiltrate of lymphocytes and sometimes of plasma cells usually occurs in the subjacent cutis (fig. 3*a* and *b*).

Arsenical epitheliomas occurring on the trunk independently of keratosis are multiple lesions of varying size, with seborrhea-like or verrucous crusts, the removal of which uncovers a wide, rolled, pearly, indurated border (fig. 4). The histopathologic picture is identical with that of epithelioma arising from arsenical keratosis, with the exception that basal cell epithelioma occasionally appears in arsenical epithelioma on the trunk. Hyperkeratotic and para-

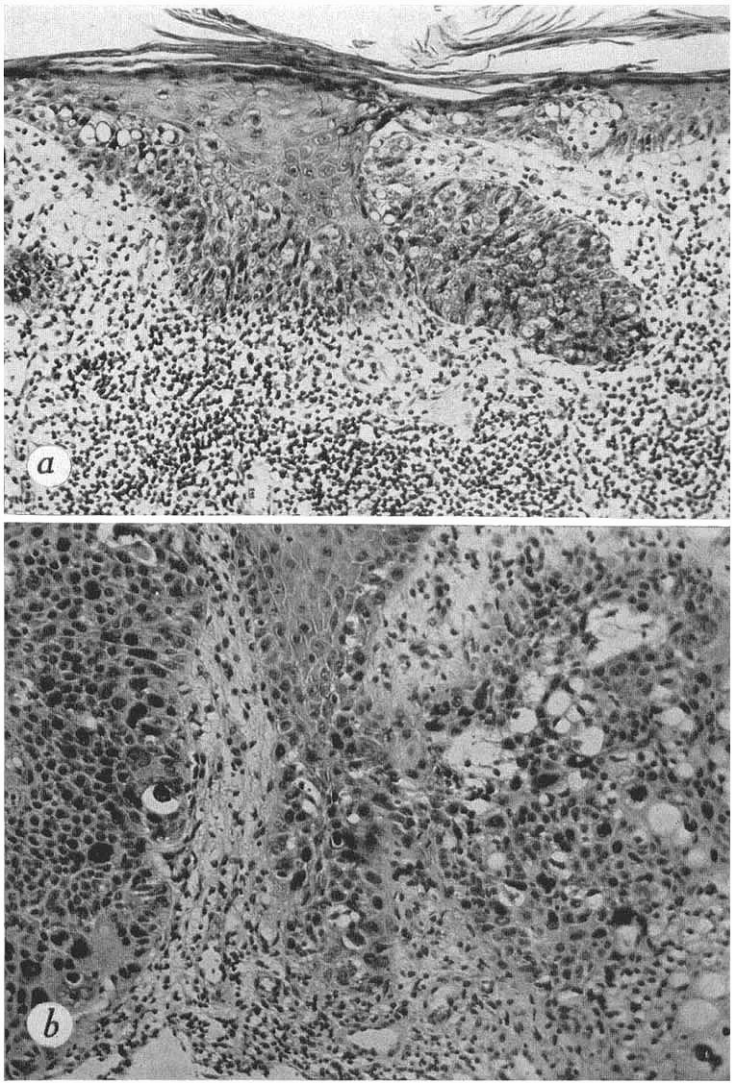

FIG. 3*a*. Arsenical epithelioma of trunk simulating Bowen's disease. Histologically early squamous cell epithelioma, grade 3, with marked vacuolation of some of the cells and dense infiltrate in the upper cutis; *b*, arsenical keratosis, squamous cell epithelioma, grade 3, which has penetrated deep in the cutis but retains all the phenomena of individual cell keratinization with abnormal mitosis, giant cells and vacuolar changes in other cells.

keratotic scales often are heaped over the lesion; rete ridges which are irregularly acanthotic, appear elongated, broadened and bulbous. Proliferation of prickle cells takes place in a disorderly crowded arrangement, with resulting variability in size and staining plus the aforementioned features of individual-cell keratinization, mitotic and amitotic cell division and vacuolation (fig. 3*b*).

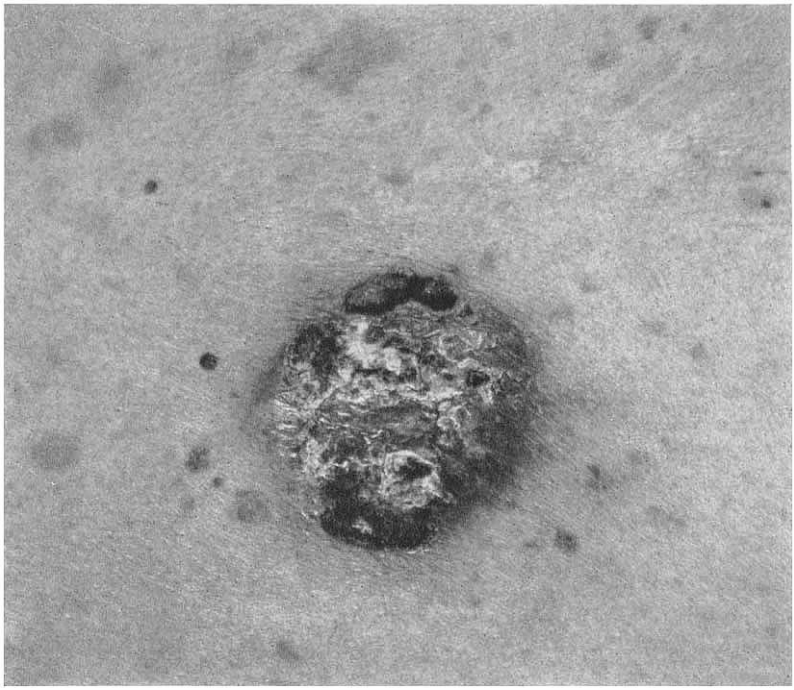

FIG. 4. Large arsenical epithelioma from back of patient who had multiple lesions; histologically squamous cell epithelioma, grade 2. Note elevation and wide, rolled border of the lesion and eczematoid and crusted epitheliomatous plaques adjacent to the large lesion.

Recently Goeckerman and Wilhelm (8) published a report on arsenical cancer of mucous membrane, which they suggested might be more common than is generally considered, if the lesion develops in the absence of classic cutaneous epithelioma. We

have had under observation a patient who had two arsenical carcinomas of mucous membranes (9). This case was reported (as case 2) in the earlier study by the senior author in 1935. An abstract of the complete history follows:

Case 4. A farmer, aged forty-two years, was first seen at the clinic in 1927. A tumor of the left sole arose from an arsenical keratosis. The lesion proved to be squamous cell epithelioma, grade 3. Treatment consisted in excision of the lesion, followed by application of radium to the enlarged inguinal nodes.

During the following seven years numerous superficial epitheliomas of the arsenical type developed on the trunk. In 1934 these were found to be squamous cell epitheliomas of grade 1 and grade 2, in which crystals of arsenic were demonstrated by Osborne's stain. Also present was one superficial epithelioma, which histologically was a basal cell cancer. At the same examination the patient was found to have an intra-urethral epithelioma, grade 3, of the arsenical type. Partial amputation of the penis was performed.

In 1938 the patient returned. Bronchoscopic examination disclosed a tumor of the bronchus. Microscopically this was found to be epithelioma, grade 4, with vacuolation of cells and malignant dyskeratosis characteristic of the arsenical type of epithelioma. The patient died in February, 1940 of extensive metastasis.

In addition to the feature of arsenical carcinomas arising on mucous membranes, this case also illustrates the benign prognosis with regard to cutaneous tumors observed during a total period of thirteen years, as well as with regard to the intra-urethral tumor which showed no evidence of recurrence up to the patient's death six years later.

DIFFERENTIAL DIAGNOSIS AND PROGNOSIS

Bowen's disease (3) is characterized clinically by solitary lesions with arciform configuration or by multiple lenticular plaques simulating the nodulo-ulcerative syphiloderm. Undoubtedly this picture may be simulated by the arsenical epithelioma. The histologic structure which is not unique but is found also in other precancerous dermatoses is that of squamous cell epithelioma in situ, with features of abnormal keratinization of individual cells, clumping of cells to form epithelial giant cells, and amitotic cell division producing giant epithelial cells; all these are phenomena of so-called malignant dyskeratosis. Vacuolation of cells also may be present, but usually this feature is not so prominent as it is in arsenical epithelioma.

Superficial epitheliomatosis (2) includes grossly two types of lesions, the "dry" form, usually basal cell epithelioma, and the "moist" or eczematoid form, usually basal squamous or squamous cell epithelioma (fig. 5). The fine, threadlike, rolled pearly border and the relative lack of induration characterize the individual

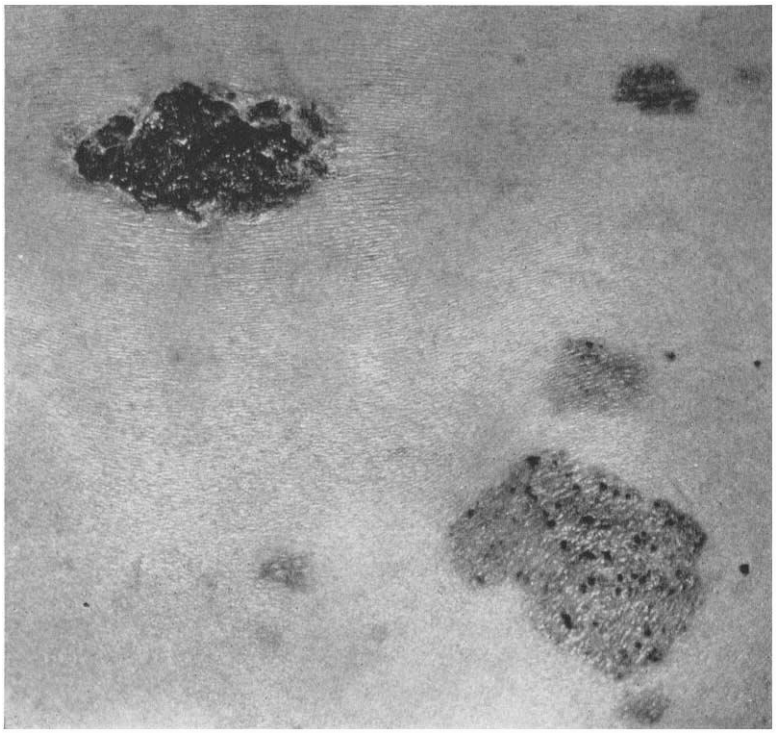

FIG. 5. Lesions of superficial epitheliomatosis of seven years' duration from a man, aged sixty-one years. The upper moist eczematoid lesion histologically is a basal squamous cell epithelioma. The other dry lesions are typical for superficial epitheliomatosis. In the large dry lesion a fine threadlike pearly border can be discerned.

patches, among which the basal cell form is the more common. Histologic Bowen-like changes occur only exceptionally in superficial epitheliomatosis (10); the case published by Voss (11) probably represents such an occurrence rather than the presence of actual arsenical cancers. The wide, rolled, indurated border of

the arsenical epithelioma makes for ready distinction from the patch of superficial epitheliomatosis. Contrary to Anderson's (12) observations, a history of ingestion of arsenic is rarely obtained, nor is arsenic usually found within the tissues of superficial epitheliomatosis.

For the purpose of prognosis it is important to distinguish arsenical epitheliomas from the lesions of superficial epitheliomatosis and Bowen's disease. The work of one of us (2) (H. M.) has indicated the relatively benign character of superficial epithelioma. It also has been shown that, although penetrating epithelioma will develop in approximately 20 per cent of cases of Bowen's disease, the lesion may be present for years and even decades without increase in size. The degree of malignancy of epitheliomas attributable to arsenic as determined histologically, is usually of grade 2 or 3, but the clinical course is generally that of squamous cell epithelioma of grade 1 or 2. They are therefore somewhat of an exception to the rule of parallelism between the histologic grading (Broders) and the clinical course of malignancy. This aspect of the arsenical epithelioma may require further study. Arsenical epitheliomas, although not usually of a high degree of malignancy in their behavior, more often lead to invasive growth and metastasis than the majority of cases of Bowen's disease.

TREATMENT

Radical measures, consisting either of surgical removal or destruction by cautery, constitute the most satisfactory treatment for the arsenical epithelioma. Experience has indicated repeatedly the inadequacy of radiotherapy in these cases, recurrences often following application of large doses of radium or roentgen rays to the lesions. Periodic re-examinations of the skin for the detection and treatment of early new lesions is an essential procedure in every case.

COMMENT

One of us (1) (H. M.) previously expressed the opinion that in cases of epithelioma specifically provoked by arsenic, the arsenic can be demonstrated in the tissues by chemical or by histochemical

procedures. Further experience has indicated to us that, because of the small quantities of arsenic which are often present in the specimen, the quantitative microchemical determination sometimes may yield negative results. The minute quantities of arsenic reported in some specimens probably signify that in these cases the amounts of arsenic are just on the threshold of analytic detection.* So far we have not encountered any sections of arsenical epithelioma in which treatment by Osborne's method has not succeeded in demonstrating the characteristic crystals in the tissue, regardless of the results of chemical analysis. The same cannot be said for all cases of superficial epitheliomatosis.

Indeed, in a series of cases of superficial epitheliomas which we observed, no arsenic whatever was detected in the tumors in the majority of cases. This fact might be interpreted as providing some argument against the rôle of arsenic in the pathogenesis of superficial epitheliomatosis. For the proper evaluation of the crystals in the tissues, we cannot recommend too emphatically the necessity for applying the diagnostic criteria described by Osborne (6, 13).

In a "control" series of tissues studied we have established a high correlation between the results of the histochemical and chemical technics. Although we have yet to encounter tissue in which, with a positive chemical test, arsenic cannot be demonstrated histologically, the converse does not hold, for often the Osborne test gives positive results when the results of chemical analysis are negative, just as occasionally happens in arsenical epithelioma.

In the few cases in which we found arsenic in lesions of super-

* We feel, contrary to the findings of Tannenholz and Muir (Tannenholz, Harold, and Muir, Kathleen B.: Methods for microchemical demonstration of arsenic in tissues, Arch. Path., **15**: 789, 1933), that Osborne's technic is very sensitive for demonstrating traces of arsenic in amounts too small to yield positive results on quantitative chemical tests. The qualification must be re-emphasized, however, that the identification of crystals of arsenic trisulfide is not a simple matter, for the Osborne technic is sometimes capricious, and artefacts may mislead the inexperienced observer. Considerable practice is required to distinguish with facility the greenish yellow, haloed, refractile particles of arsenic trisulfide from granules of pigment and other forms of extraneous depositions in the skin.

ficial epitheliomatosis, the quantity of the arsenic was practically always less than in the adjacent normal skin, whereas in the arsenical epitheliomas the quantity of the arsenic is more than in the adjacent normal skin. Since arsenic may be demonstrated frequently in tissues even in the absence of a satisfactory history of exposure to the agent, it is not surprising to find it occasionally in some lesions of superficial epitheliomatosis; nor does this finding weaken our conclusion with regard to the distribution of arsenic in the arsenical epithelioma. Also the hypothesis of Fischer-Wasels (14) must be recalled, that arsenic acts as an activator of latent cancerous foci in the skin. Invoking this concept, one of us (3) (H. M.) has attempted to explain why both arsenical and superficial epitheliomas at times occur together in certain subjects after exposure to, or ingestion of, the drug, or why areas of basal cell epithelioma appear adjacent to areas of squamous cell epithelioma.

As reports in the new and older literature attest, the opportunities for exposure to arsenic are numerous. Boos and Werby (15) and Cannon (16) recently enumerated possible food sources for the ingestion of arsenic, and Barksdale (17) has implicated tobacco as a cause for arsenical reactions in the sensitized skin. Undoubtedly the medicinal administration of arsenic accounts for the provocation of epithelioma in the majority of cases, but in cases in which no adequate history is provided to indicate the source, the ingestion or inhalation of minute quantities of arsenic through food, tobacco or industrial exposure may be sufficient to precipitate characteristic precancerous and cancerous changes in the skin of some predisposed persons.

SUMMARY AND CONCLUSIONS

The concept that arsenical epithelioma is associated with a local concentration of arsenic in the tissue is confirmed by examination of additional material. In contrast with this finding, the lesions of superficial epitheliomatosis usually show no evidence of accumulation or storage of arsenic. We have indicated the value of the histochemical method for demonstrating arsenic in the tissues to supplement the procedure of direct chemical analysis.

Clinical and histopathologic distinctions of arsenical epithelioma from superficial epitheliomatosis and Bowen's disease are drawn, to emphasize the practicality of regarding each disease properly as a separate entity. Epithelioma provoked by arsenic usually is relatively benign, and case histories are cited which illustrate this point.

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DISCUSSION

DR. S. W. BECKER, *Chicago*: The authors are to be congratulated on having such a large number of arsenical carcinomas to study. In our Clinic we have had very few. One point should be considered in some detail. The conclusions presented were based on the apparent finding of arsenic by the hydrogen sulfide method. This method was introduced many years ago, and has been used by several workers, notably Osborne, in this country.

As one reads the very early work, the method was not properly controlled. Some years ago, in 1933, in our Clinic, we undertook some arsenical studies and used this method. To our surprise we found the same crystals in the controls as in the abnormal specimens. For two years we tried to find out what was wrong with the method, and to prove that this was arsenic. We were not able to do so. At the same time in Vienna, another group tried to prove this, and two papers (Tannenholz, H., and Muir, K.B.: Methods for Microchemical Demonstration of Arsenci in Tissues, Arch. Dermat. & Syph., **15**: 789 (June) 1933. Oppenheim, M., und Fantl, P.: Ueber Hauterkrankungen, verursacht durth arsenhaltige Wandfarben II. Versuche zum histologischen Nachweis von Arsenverbindungen in der Haut, Archiv. f. Dermat. u. Syph., **170**: 488, 1934.) appeared with the same conclusions. Dr. Oppenheim, working with Dr. Fantl, made a more extensive study than ours, and I think it appropriate to hear from Dr. Oppenheim.

DR. MAURICE OPPENHEIM, *Chicago*: I wish to thank Dr. Becker for mentioning my work in collaboration with Dr. Fantl. We published 3 papers in the Archives of Dermatology, Biology and Physical Chemistry on this subject. Dr. Montgomery has shown us a great number of cancers caused by arsenicals, and we can confirm this, especially in occupational cases, in certain trades, as feather dyers, animal stuffers, and all people dealing with arsenical compounds, and those staining wall papers, using wall dyes, living in rooms covered with arsenicals contained in wall dyes and wall papers. Sometimes we see the originating warts, and later the cancers.

It was very peculiar for us to find that if we used arsenic in therapeutic doses given over long periods continually for months and years, in cases of neoarsphenamine used in syphilis also, we never saw this. We made experiments and found that the effect of arsenic on the skin is definite. Some compounds of arsenic are accumulated in the hair, nails and scales, in the horny part. In other cases it affects the pigment in epidermis and cutis, which has a definite affinity for arsenic.

As you know, arsenical melanoses are a very common observation. We found out that the various arsenic compounds have varying degrees of affinity for the tissues of the skin. In our investigations we found all the methods used to prove the presence of arsenic in the skin by microchemical methods are to be doubted. Fantl and I carried out experiments in vitro in animals and man, and we could not definitely find the yellow transparent crystals—nothing was found in the connective tissue. Therefore we are doubtful if any of these cases quoted by Dr. Montgomery as having all these findings are really arsenic. The same held true for the

microchemical histological proof of mercury in the skin which was studied by Justus in Hungary. So we are very critical concerning the proof of arsenicals by microchemical methods.

It must be a certain kind of arsenic, which causes cancer. We see the same in tar cancer. Not all tars cause cancer of the skin. And in the same way, perhaps, a certain type of arsenic is causing arsenical cancers, another, rather melanosis, a third one more hyperkeratosis etc. I could not find in this country, skin disorders caused by wall dyes and wall papers containing arsenic as it is the case in Austria, where the occasion of arsenic intoxication is much greater, and consequently more cases of chronic arsenic intoxication are observed, but we could not ascertain in which way or form arsenic was absorbed from wall dye and wall paper. It would be very interesting if we could find out.

I am sorry that our investigations were interrupted by the political conditions. I present only one slide showing arsenical cancer of the heel of a feather dyer with arsenical dyes; this was a prickle cell cancer, which is usually observed in cases of chronic arsenic intoxication. The hyperkeratosis was not as intense as we are accustomed to see it.

DR. NELSON PAUL ANDERSON, *Los Angeles*: I think that the only fact that Dr. Montgomery and I agree on in this matter is that the kerotoses appearing on the palms and soles are due to arsenic. From then on we rapidly diverge. My impression, since the first work done in 1932, is that the great majority of cases of so-called superficial epitheliomas of the trunk are due to arsenic. I have had no reason to change that opinion.

In the past 9 years I have observed at least 39–40 cases of superficial epitheliomas in which arsenical keratoses were present on the palms and soles. Whether one accepts this as evidence of arsenical origin makes very little difference. It is very peculiar, however, that this circumstance happens. I think Dr. Goeckerman performed a great service last year in calling attention to the fact that arsenic should be looked upon as a causative factor in some mucous membrane epitheliomas. He presented a case of papillomas of the bladder and multiple epitheliomas of the body and arsenical keratoses of the palms and soles, but on looking back into the literature you find that this is not so uncommon.

At the time of Dr. Goeckerman's presentation, Dr. Everett C. Fox of Dallas mentioned Dr. Fraser's case, which we both treated. This patient was treated only once a month, because he was being treated for papillomas by a urologist. Later, Dr. Goldman and Dr. Tauber presented a case of superficial epitheliomas in the British journal of Dermatology in which they described one of their patients as suffering from papillomatosis of the bladder. I believe that this feature of arsenic in mucous membrane carcinoma is being neglected.

A third point I would like to make, is one I have only recently run across. I am sure you are all familiar with the phenomenon of fluoride mottling of the teeth. I do not wish to malign Texas, but this particular patient I saw came from Texas; she had arsenical keratosis of the palms and soles, and also fluoride mottling of the teeth. I do not know whether this has any significance or not. It is just an isolated clinical observation.

I have done no further work on superficial epitheliomas since my original work in 1932, but at that time I made this observation, which was not published, and

should have been. Instead of using normal controls with Osborne's microchemical method, I used warts and mucous membrane cancers, including cancers of the tongue. It was very surprising that positive results were obtained with cancers of the mucous membranes, and with ordinary verruca vulgares.

Is there really arsenic in such lesions? Do these lesions have a sort of arsenotropism, e.g., do they pull arsenic in them? I do not know.

DR. THEODORE CORNBLEET, *Chicago*: The frequency with which arsenic keratoses occur on the palms and soles makes one think that perhaps there must be some relationship to sweat; indeed sweat contains a great deal of arsenic, and is one of the major routes for the excretion of arsenic. Of course, hair, nails and other sites of skin contain arsenic. I wonder if there is not something in oil-bearing areas which tends to inhibit somewhat the formation of keratoses and epitheliomas from arsenic. It is an interesting point to follow up.

Arsenic, like halogens, takes a long time to excrete. One can examine a patient with a disease due to arsenic and find it coming through after 30–50 and more days, just as do the halogens. In several patients, to whom I have given test doses of arsenic, and observed the length of time it took to excrete this, I found that those that have arsenical keratoses take a longer time to excrete a given amount of arsenic than that taken by my control patients. That is perhaps noteworthy because it may be that arsenic is retained in the epidermis for protracted periods—for too long an interval in some cases, so as to irritate and produce those changes we find in arsenical keratoses and epitheliomas.

I am also inclined to speculate about Dr. Montgomery's findings in regard to some epitheliomas having no arsenic at all, and some having more than the control studies. I should like to ask: 1) are these epitheliomas examined long after arsenic had been taken; perhaps all the arsenic had already been excreted, but the keratoses and epitheliomas continued once initiated; and (2) one should correlate the amount of epidermal tissue, that is, the number of cells in the epithelioma with that in the control sites. Of course, where there are more cells present, as in epitheliomas and keratoses, one would expect to find a greater accumulation of arsenic.

DR. MORRIS WAISMAN, *Chicago*: I should like to answer the arguments questioning the value of the histochemical method for the detection of arsenic. The majority of lesions of superficial epitheliomatosis in our material showed arsenic to be absent both by direct chemical analysis and by histochemical examination. We were impressed by this correlation between the two methods and particularly by the specificity of the latter procedure, that is, the Osborne technic. Another observation that cannot be ignored is our finding of characteristic crystals in sections of every cutaneous lesion in which direct chemical analysis confirmed the presence of arsenic. Moreover, in the arsenical epitheliomas, where chemical examination shows the arsenic to be concentrated in the tumor as compared with the adjacent normal epidermis, we found by Osborne's method a parallel concentration of crystals within the epithelioma, with fewer crystals or none in the neighboring epidermis. These results make a strong case for the dependability of the histochemical findings.

It should be emphasized again that the interpretation of refractile granules

under the microscope is a difficult task, and that strict criteria must be employed for distinguishing crystals of arsenic trisulfide from various adventitious particles which may be visible in a section of tissue. Of course the quantitative chemical method is not liable to this same subjective handicaps. In our study we found by the quantitative (Gutzeit) method generally more arsenic within the arsenical epithelioma than in the adjacent skin, and we have simply reported the fact, which confirms the conclusion reached by Dr. Montgomery in 1935. We obviously did not undertake to reinvestigate Osborne's work, but we are satisfied from the comparison with our quantitative data that Osborne's method is reliable for the detection of small amounts of arsenic in the tissues.

Dr. Hamilton Montgomery, *Rochester, Minn.*: Arsenic is definitely a carcinogenic substance and pentavalent arsenic has an affinity for the epidermis. Ebert showed that local application of arsphenamine to the skin could result in Bowen-like changes. Rarely have arsenical keratoses appeared following use of trivalent arsenicals including arsphenamine. Some physicians hesitate to use arsenicals in the treatment of syphilitic leukoplakia because of the danger of precipitating true malignant change. Arsenic may be demonstrable in the tissue thirty years or more after the patient has stopped taking arsenic. We believe Osborne's modification of the Brunauer method for determining arsenic in tissue to be a reliable one if done on fresh tissue and freshly fixed formalin. The method had been controlled and checked against quantitative chemical analysis by Osterberg's modification of Gutzeit's method. More arsenic can usually be demonstrated in areas of arsenical epithelioma or arsenical keratosis than in adjacent normal skin. In answer to Doctor Cornbleet, the amount of arsenic demonstrated is many times in excess of the amount that would be regarded as the upper limits of normal arsenic content of the skin, even of persons with a known exposure to arsenic in various forms.

The majority of cases of superficial epitheliomatosis give no history of ingestion of arsenic and none can be demonstrated by either method of chemical analysis. In about 15 per cent of our cases, both lesions of superficial epitheliomatosis and arsenical epithelioma were present in the same individual. Discrepancies between our figures and those of Doctor Anderson may be on the basis that in the part of the country from which his cases come the patients may be exposed to arsenic. Arsenic as a carcinogenic substance can stimulate latent or dormant foci of epithelioma and thus explain the combination of the two types of superficial epitheliomas in the same individual.